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ADENOCARCINOMA OF THE PROSTATE WITH ECTOPIC ANTIDIURETIC HORMONE PRODUCTION : A CASE REPORT

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An 88-year-old patient with a poorly differentiated adenocarcinoma of the prostate gland was found to have all cardinal findings of syndrome of inappropriate antidiuretic hormone secretion (SIADH). Elevated levels of antidiuretic hormone were found in the patient's serum and in the prostatic tumor and the cytoplasm of the tumor was positive for prostate specific antigen and was faintly positive for antidiuretic hormone (ADH). He responded well to combination therapy of androgen blockade with leuporelin acetate and flutamide, and laboratory findings of SIADH and serum ADH level returned to normal. However, he died of sudden profuse bleeding caused by gastric ulcers 6 months after the therapy. Ten cases of SIADH caused by prostatic cancer have been reported including the present case.

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Key words : Prostate, Adenocarcinoma, Inappropriate ADH syndrome, Ectopic hormone production

INTRODUCTION

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) was initially reported by Schwartz et al.¹⁾ in 1957. In 1973, Bartter²⁾ revised cardinal findings as follows: 1) hyponatremia, 2) urinary solute concentration higher than plasma solute concentration, 3) excretion of sodium in the urine, 4) depression of plasma renin despite hyponatremia, and 5) normal renal function. SIADH can occur in patients with a variety of diseases, including malignant tumors, pulmonary diseases, central nervous system disorders, and drugs³⁾. Adenocarcinoma of the prostate is a rare cause of this syndrome, with only 9 reported cases^{3–11)}. We report a case of SIADH induced by adenocarcinoma of the prostate.

CASE REPORT

An 88-year-old man presented with urinary retention. Physical examination revealed a stony hard prostate with enlargement. Laboratory tests demonstrated serum sodium 120 mEq/l (normal 135 to 145), serum osmolality 250 mOsm/kg (normal 275 to 295), plasma renin activity 0.1 ng/ml/h (normal 0.2 to 2.7), serum antidiuretic hormone (ADH) 7.5 pg/ml (normal 0.3 to 3.5), creatinine clearance 73.5 ml/min, urine sodium 108 mEq/l and urine osmolality 559 mOsm/kg. Serum prostate specific antigen (PSA) was 862.0 ng/ml (normal less than 4.0). Dehydration was denied because of the following findings: normal moisture of skin and lips was kept, blood

pressure was 120/70 mmHg, heart rate was 84/min, laboratory values of hematocrit, total protein, blood urea nitrogen, creatinine, uric acid and fasting blood sugar were normal. Results of a complete endocrine evaluation, including thyroid function tests, serum cortisol, drug screening and head and chest computerized tomography were normal. Ultrasound-guided transrectal needle biopsy of the prostate revealed a poorly differentiated adenocarcinoma (Fig. 1), that is, neoplastic cells showed small nests or fascicular arrangement in the muscle layer. On immunohistochemical examination, in which rabbit anti-PSA from Dakopatts (Glostrup, Denmark) were used, the cytoplasm of the tumor cell was positive for PSA (Fig. 1). Although the tumor appeared different from that shown in figure 1 and

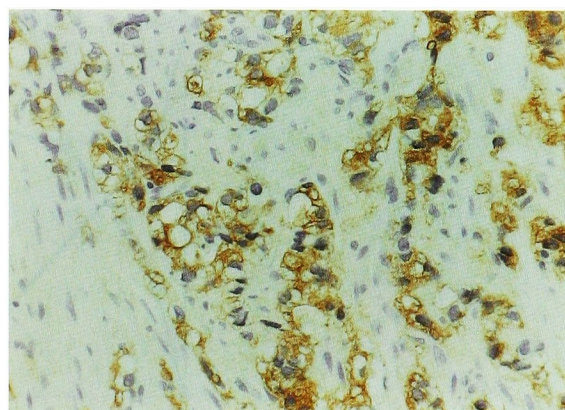


Fig. 1. Immunohistochemical finding of the tumor showing cytoplasmic PSA immunoreactivity (reduced from $\times 320$).

showed a moderately differentiated adenocarcinoma instead of a poorly differentiated adenocarcinoma, the cytoplasm of the tumor cell was faintly positive for ADH on immunohistological examination using rabbit anti-ADH from ICN Biomedicals Inc. (Costa Mesa, California, USA) (Fig. 2). The ADH concentration in the prostatic specimens obtained by transrectal biopsies was 54.0 pg/mg wet weight using a radioimmunoassay technique. Bone scan revealed multiple metastatic lesions. From all these findings the diagnosis of SIADH caused by prostatic cancer was made.

The patient was treated with combination therapy of androgen blockade with a luteinizing hormone-releasing hormone (LH-RH) agonist and flutamide. The serum sodium level and serum osmolality gradually increased after initiation of therapy, while the urine sodium level, urine osmolality, the serum PSA level decreased (Fig. 3). Ninety days after the

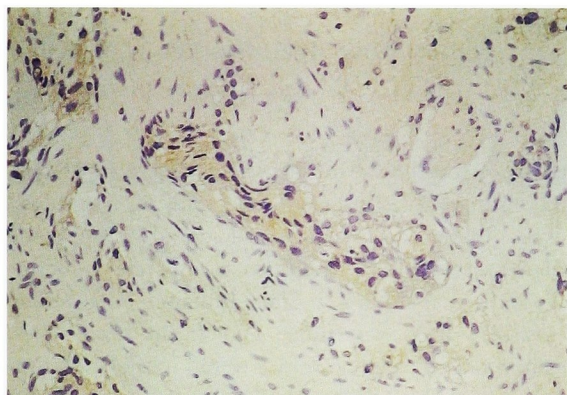


Fig. 2. Immunohistochemical finding of the tumor showing faintly positive cytoplasmic ADH immunoreactivity. The field was different from figure 1 (reduced from $\times 320$).

beginning of hormone therapy, laboratory tests demonstrated serum sodium 139 mEq/l, serum osmolality 280 mOsm/kg, urine sodium 18 mEq/l, urine osmolality 275 mOsm/kg, plasma renin activity 0.3 ng/ml/h, serum ADH 0.8 pg/ml (Fig. 4) and serum PSA 2.5 ng/ml. However, he died of hemorrhagic shock due to sudden profuse bleeding caused by a gastric ulcer at a local hospital 6 months after the therapy.

DISCUSSION

In 1928, the first case of a patient with a hormonally induced paraneoplastic syndrome was reported by Brown¹²⁾ who described an ectopically induced adrenal hyperplasia later known to be caused by ACTH produced by tumor cells. Later, other paraendocrine syndromes have been described, amongst them SIADH. The first clinical cases of SIADH were presented by Schwartz et al.¹⁾ in 1957, who described two patients with lung cancer who developed hyponatremia associated with continued urinary sodium loss. They noted that the syndrome was similar to what occurred when normal individuals were given ADH. They postulated that the tumors led to the inappropriate release of ADH, later discovered to consist of arginine-vasopressin. Differential diagnosis of SIADH includes malignant tumors, disorders involving the central nervous system, intrathoracic disorders and drugs. In malignant tumors, oat cell carcinoma of the bronchus is the most frequent, followed by lymphoma, cancer of the pancreas, duodenum, adrenal gland, ureter and thymus, and sarcoma of stomach^{3,8)}.

Adenocarcinoma of the prostate is a rare cause of this syndrome, with only 10 reported cases including the present case (Table 1). Although we were unable to present an electro-microscopic examination

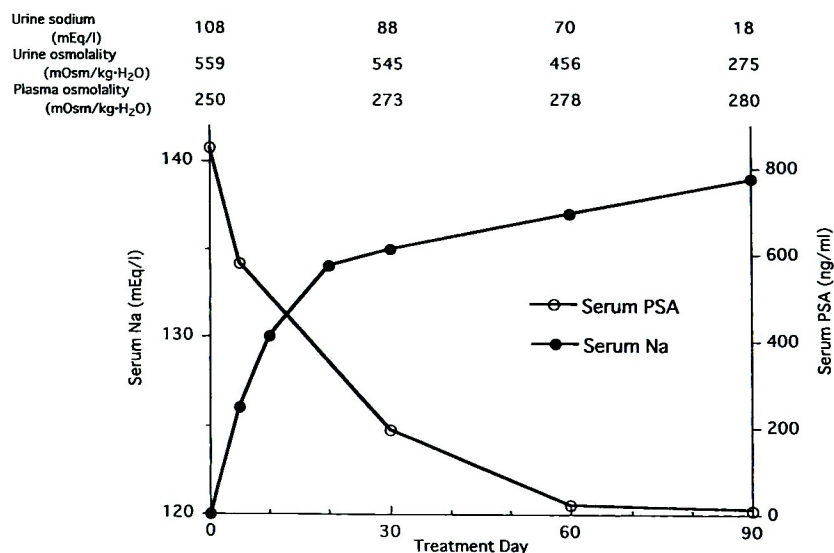


Fig. 3. Longitudinal change of levels of serum sodium, serum osmolality, urine sodium, urine osmolality and serum PSA.

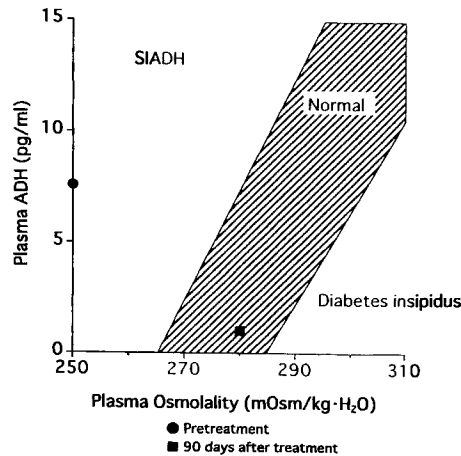


Fig. 4. Relationship between plasma ADH and osmolality.

and the cytoplasm of the tumor cells was only faintly positive for ADH, we thought our case was worth reporting because of the rarity of this disease, fulfillment of cardinal findings and high level of ADH in the prostatic tumor. Three recent papers showed neither immunohistochemical examination nor electro-microscopic examination^{3,9,10)}

The tumor stage was D in most cases and Gasparini et al.³⁾ reported that their case was the first case without bone metastasis. The serum ADH level was measured in 7 cases; the ADH concentration in prostatic tumor tissue in the case reported by Sacks et

al.⁵⁾ and the present case was 43.0 and 54.0 pg/mg, respectively.

Hormone therapy with estrogen was performed in 2 cases, hormone therapy with estrogen and castration performed in 3 cases, LH-RH agonist was given in 2 cases, and LH-RH agonist and flutamide were given in the present case. The method of treatment was not clearly described in 2 cases.

Serum ADH level was normalized in only one previous case³⁾ and the present case (Fig. 4), in which an LH-RH agonist, and LH-RH agonist plus flutamide were used, respectively. Gasparini et al.³⁾ mentioned that the possible role of LH-RH antagonists-agonists on the posterior pituitary or supraoptic and paraventricular nuclei of hypothalamus remains to be elucidated, although they realized that LH-RH antagonists-agonists appear to have a primary effect of down regulating receptors of the anterior pituitary. The prognosis of these 10 cases was poor as follows: three patients died of pneumonia⁴⁾, prostatic cancer⁵⁾ and pulmonary embolism⁶⁾ one month after onset of SIADH, one patient died of prostatic cancer 2 months after the onset⁷⁾, one patient died of renal failure 3 months after the onset⁹⁾, one patient (present case) died of gastric ulcer 6 months after the onset, and one patient died of prostatic cancer 12 months after the onset⁸⁾. The mean survival time was 3.71 ± 4.07 months in 7 patients. In the other 3 cases⁷⁻⁹⁾, the prognosis was

Table 1. Reported cases of SIADH secondary to carcinoma of the prostate

Reference	Patient age (yrs.)	Tumor Stage	Tumor Grade	Plasma ADH (pg/mg)	ADH level in the tumor (pg/mg)	Treatment	Response to therapy*
Sellwood ⁴⁾ (1969)	51	D	Poorly differentiated adenocarcinoma	6.3–12.5	Supraculavicular lymph node (250)	Estrogen and castration	Died of pneumonia (1 month)
Sack et al. ⁵⁾ (1975)	60	D	Poorly differentiated adenocarcinoma	27.0	Prostate (43.0)	Estrogen and castration	Died of prostate cancer (1 month)
Heim et al. ⁶⁾ (1977)	71	D	Poorly differentiated adenocarcinoma	27.0	ND	Estrogen	Died of pulmonary embolism (1 month)
Vossli et al. ⁷⁾ (1981)	66	ND	Adenocarcinoma	ND	ND	Estrogen	Died of prostate cancer (2 months)
Murakawa et al. ⁸⁾ (1984)	72	D	Adenocarcinoma	3.8	ND	Estrogen and castration	Died of prostate cancer (12 months)
Ghandur-Mnaymneh et al. ⁹⁾ (1986)	73	D	Undifferentiated small cell carcinoma	ND	ND	LH-RH agonist	Died of renal failure (3 months)
Osterling et al. ¹⁰⁾ (1992)	ND	ND	Undifferentiated small cell carcinoma	5.3	ND	ND	ND
Gasparini et al. ³⁾ (1993)	59	C	Moderately differentiated adenocarcinoma	3.3	ND	LH-RH agonist	ND (Survived at least 3 months)
Pereira Arias et al. ¹¹⁾ (1995)	58	D	Moderately differentiated adenocarcinoma	ND	ND	Hormone therapy	ND
Present case (1999)	88	D	Poorly differentiated adenocarcinoma	7.5	Prostate (54.0)	LH-RH agonist and flutamide	Died of gastric ulcer (6 months)

* Cause of death and duration of survival after the onset of SIADH, ND: not described.

not described.

Because of prevalence of preventive medicine for cancer of the prostate mainly using examination of serum PSA level, ratio of advanced cases of cancer of the prostate to early stage is decreasing, but with a higher awareness of SIADH, an increasing number of prostatic cancer cases with this syndrome may be found in future.

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和文抄録

異所性抗利尿ホルモン産生を呈した前立腺癌の1例

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症例は88歳，男性で尿閉を主訴とし，前立腺特異抗原（PSA）値，直腸診所見から前立腺生検を施行し低分化型腺癌と診断さる．血液生化学検査の結果，抗利尿ホルモン（ADH）分泌異常症候群診断基準を満たしていた．また血中および前立腺癌組織中のADH値の上昇を認め，免疫組織化学的検査において腫瘍細胞はPSAに陽性で，ADHに対しても軽度陽性で

あった．酢酸リュープロレリンとフルタミドによる抗アンドロゲン療法に反応し，90日後には血液生化学所見も正常となったが，治療開始6カ月後に胃潰瘍からの大量出血により死亡した．異所性ADH産生性前立腺癌症例は本症例を含め10例目の報告である．

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